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THE CHARACTERS AND METHODS OF ASSAY  
OF THE  
OFFICIAL HYPOPHOSPHITES  
AND A  
NOTE ON THE MYDRIATIC ALKALOIDS

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# THE CHARACTERS AND METHODS OF ASSAY OF THE OFFICIAL HYPOPHOSPHITES.\*

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It is generally recognised that the methods at present known and employed for determining the amount of hypophosphite contained in the commercial salts are unsatisfactory. The object of this investigation was, therefore, to devise an accurate method for such determinations, and having accomplished this, it was thought of interest to supplement its description with an account of some of the properties of the various hypophosphites prepared for the purpose of this inquiry.

Hypophosphorous acid was discovered in 1816 by Dulong, and several of its salts were prepared and their properties examined by Rose. Those of interest to the pharmacist and dealt with in this paper are the potassium, sodium, calcium, barium, iron, and manganese salts. The calcium and barium salts are obtained directly, being obtained by evaporation from the resulting aqueous solution. The sodium and potassium salts are prepared by double decomposition from the calcium salt, and may be purified by crystallisation from alcohol, in which both are soluble. The iron and manganese salts can also be prepared by double decomposition or by general methods, but they are insoluble in alcohol. All the hypophosphites are more or less soluble in water, and are easily oxidised to phosphites and ultimately to phosphates. Impurities may be detected by the ordinary reagents, phosphite being

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detected by the reaction with barium chloride or lead acetate, since barium phosphite is but slightly soluble in water, and lead phosphite insoluble.

P. de St. Gilles first proposed to assay hypophosphorous acid or its salts by titration with potassium permanganate, stating that the oxidation was easily accomplished, whilst Rose proposed the oxidation of the acid by mercuric chloride, and determination of the amount of hypophosphorous acid present by weighing the calomel formed.

In 1887 Lunan (*P.J.*, 1887, p. 773) in examining the acids rejected the permanganate method and adopted the calomel assay method, but did not give any reason for this, nor are any data given to show the accuracy of the latter method.

In 1889 Moerk (*A.J.P.*, 1889, pp. 326, 386, 459) published a lengthy paper dealing with the qualitative and quantitative examination of hypophosphorous acid and such of its salts as are largely used in America. In addition to the permanganate and calomel methods, he assayed the salts by first oxidising with bromine, and then determining either the hydrobromic acid or the phosphate formed, by general methods. He found the permanganate method unsatisfactory, as a brown precipitate is formed even in acid solution, which only slowly oxidises the phosphite. Good results were, however, obtained with the calomel and bromine methods. No evidence of the accuracy of these methods is given, and apparently impure material was used, as in the course of the paper it is mentioned that unsatisfactory results were obtained owing to "the alkaline hypophosphites containing probably chlorides," and a correction is introduced in a later paper for the impure bromine used for oxidation. Assuming that concordant results were obtained, this is no proof of the accuracy of the methods, and it is not stated that even these were obtained. In the qualitative examination of several salts, phosphite was only met with in one case, viz., a potassium salt stated to contain 13 per cent. of phosphite, and which gave no precipitate with lead acetate and acetic acid. The evidence on which the presence of phosphite was based was a small difference in results obtained by different analytical methods. These results are contrary to published statements and my own experiments, as lead phosphite is insoluble in water acidulated with acetic acid, and it is only rarely that commercial specimens are met with which are free from

phosphite. There are other statements in the paper referred to which require modification, and one is regretfully led to the conclusion that little reliance can be placed on the author's results.

In 1891 Amat (*Compt. rend.*, cxi., p. 676) recommended the calomel method, urging that with permanganate there is a tendency to two errors : (1) By incomplete oxidation of the hypophosphite ; (2) by decomposition of the permanganate at high temperatures. He also noted the formation of a brown precipitate during titration with permanganate, which was only completely dissolved on the addition of oxalic acid.

The U.S.P. adopts the permanganate method and makes the curious mistake of requiring the oxalic acid to discharge the "red" colour, whilst in reality it is a brown precipitate which is gradually decomposed by the oxalic acid. No tests are given for phosphites, except in the case of the calcium salt, when the lead acetate test is erroneously stated to detect acid phosphate, a most unlikely impurity. The sodium salt is described as hydrated, that found in the European and American markets (with one exception) is almost anhydrous.

In 1893 Roe (*P. J.*, 1893, p. 473) pointed out that phosphites appeared to be a common impurity in commercial hypophosphites.

In 1897 Tyrer (*P. J.*, 1897, p. 150), in a paper read before this Conference, stated that the permanganate method is unsatisfactory, and pointed out that phosphites are the most likely impurity. He suggested a new method of determination, which was to first precipitate with barium chloride for the removal of phosphates, phosphites, sulphates, or sulphite, to filter, and then to estimate the hypophosphite in the filtrate by the reduction of copper sulphate. Determinations by this method are stated to be very accurate, but as no experimental data are given, it is impossible to say whether the author checked his method by analyses of pure material. It is stated that the U.S.P. method of titration gave good results, as the sulphuric acid in excess keeps the manganese in solution ; I am unable to confirm this statement, as I have always found that a brown precipitate is formed as stated by Moerk and Amat. Again, hypophosphites are stated to react with mercuric chloride in the same way whether excess of mercuric salt or of hypophosphite be present, becoming in the cold partially reduced to subchloride, and on boiling reduced to mercury.



I have found that if the mercuric chloride is in excess, calomel only is formed, but if the hypophosphite is in excess, reduction takes place to mercury. That this is so follows from the method proposed by Rose and others, and which depends on the determination of the calomel thus formed. This method is further stated to be unsatisfactory because of a tendency to complete reduction to mercury, but I have found that this is easily remedied by pouring the solution of the hypophosphite into an acid solution of mercuric chloride in excess, when the calomel is obtained quite white and with no tendency to further reduction. Finally, the new B.P. (1898 edition) adheres to the unsatisfactory tests of the old edition, and gives no method of assay, but simply directions to boil a given quantity of the salt with potassium permanganate, when, on filtration, a "nearly" colourless solution should result. It is also stated that the solution of the salt should give little or no precipitate with lead acetate, and it has been repeatedly shown that it is very seldom a commercial salt meets this requirement. Further, the standard of purity required for the permanganate test is not the same as that for the lead acetate test, for a salt that gives quite a considerable precipitate with lead acetate will yield, when tested as directed, a nearly colourless solution.

In reviewing these proposed methods of assay it will be noticed that no author adduces the necessary proof of the accuracy of the method, viz., analyses of pure material and of mixtures containing a known amount of impurity. Further, in every method except that of Tyrer no notice is taken of the well-known fact that the chief impurity present, viz., phosphite, will behave in a similar manner to oxidising agents as the hypophosphite. Any method, therefore, to be accurate must either be uninfluenced by any impurities present, or the disturbing impurities must first be removed. Since only Tyrer's method fulfils this first essential condition, it is the only one which calls for comment. His method depends for its accuracy on the completeness of the removal of the impurities by barium chloride, since if any phosphite remained in solution it would reduce the copper sulphate in the same manner as the hypophosphite. Barium phosphite, however, is slightly soluble in water, and this can be easily demonstrated by dissolving the barium hypophosphite of commerce and adding a drop of lead acetate solution, when a precipitate of lead phosphite will be

thrown down. This being the case, the method cannot be accepted as accurate, owing to the incomplete removal of impurities. It is thus clear that no method of assay previously described can be considered satisfactory.

In the method I propose, the impurities are first removed by lead acetate, lead phosphite and other impurities being insoluble in water. The excess of lead is then removed by hydrogen sulphide, and the filtrate containing the hypophosphite completely oxidised to phosphate, which is determined either gravimetrically or volumetrically by the usual methods of analysis. I have proved the accuracy of this method by the analysis of pure material and of mixtures of pure material with known amounts of likely impurities. In the course of the investigation I have prepared some pure salts and examined their properties, have made some experiments with the hypophosphites of iron, and have finally made a complete examination of the principal salts of the leading British and American manufacturers, which has afforded some interesting results.

#### EXPERIMENTAL.

**SODIUM HYPOPHOSPHITE.**—The commercial salt was purified by boiling a portion with strong alcohol, filtering, and allowing the filtrate to cool, when long, transparent, prismatic crystals, sometimes an inch in length, separated. The purity of the salt was proved by taking a concentrated aqueous solution and adding a drop of acetic acid and then a few drops of lead acetate solution. If the liquid remained quite clear it was regarded as pure, freedom from other ordinary impurities having been previously ascertained. These crystals were found to contain one molecule of water of crystallisation and to be extremely deliquescent, apparently much more so than the granular salt of commerce. Experiments were made to see if the salt could be dried without decomposition. The pure salt was heated for two hours at  $100^{\circ}$ , and afterwards for one hour at  $110^{\circ}$ , when it had ceased to lose weight, and on testing with lead acetate was found to be quite pure. Experiments were made also to see if a solution of the salt in air free water could be boiled without decomposition. This was found to be the case if the water is boiled for at least ten minutes and the salt quickly added, it then suffers no decomposition on further boiling. In the following experiments the salt was dried for one hour at  $110^{\circ}$ , experiments showing that

this procedure dried the salt completely, and without decomposition. The first experiments were made with the permanganate method as follows:—About 0.1 gramme of the dried salt was dissolved in a convenient quantity of water, 1 C.c. sulphuric acid and 50 C.c. N/10 potassium permanganate added, and the mixture boiled for fifteen minutes, then N/10 oxalic acid added till colourless, and finally N/10 permanganate till the faintest pink coloration is evident. If, on standing five minutes, the coloration is unchanged, the calculation is made from the data in the usual way. If, however, the pink coloration fades or changes to a brownish tint, the hypophosphite has not been completely oxidised, and more permanganate must be added, and the operation repeated.

The following results were obtained :—

(1)	0.072	gramme pure salt required	33.1	C.c. N/10 $\text{KMnO}_4$	=	101.1	per cent.
(2)	0.0874	„ „ „	40.2	„ „	=	101.1	„
(3)	0.1296	„ „ „	58.7	„ „	=	99.6	„

The last experiment required an hour's boiling for complete oxidation. The method not giving accurate results, experiments were made to determine the cause of error. A blank experiment showed that, under these conditions,

$$23.7 \text{ C.c. N/10 } \text{KMnO}_4 = 23 \text{ C.c. N/10 } (\text{COOH})_2,$$

proving that a portion of the permanganate is decomposed on boiling. This fact and the difficulty of completely oxidising the hypophosphite caused me to abandon this method. In addition to these two errors, there is a third, due to the presence of chlorides, which are frequently found in the commercial salt, and which reduce permanganate. As these errors give respectively too high or low results, it is possible that under certain conditions they might balance each other and give an apparently correct result.

The calomel method was next tried, though there is an initial difficulty by this method in properly drying the calomel. The solution of the pure salt was poured into a solution of excess of mercuric chloride acidulated with hydrochloric acid and the mixture heated on a water bath for one hour, and the calomel separated and weighed.

0.0438	gramme salt gave	0.4746	gramme calomel	=	101.4	per cent.
0.0934	„ „ „	1.0092	„ „	=	101.2	per cent.

These results and the difficulties of the method led to its abandonment.



The next method tried was that of oxidation and subsequent determination as phosphate. The oxidation is carried out by bromine, or better, by potassium chlorate and hydrochloric acid in the usual way, and the resulting phosphate estimated gravimetrically or volumetrically by the usual analytical methods. The results thus obtained were very accurate.

0.3096 gramme pure salt	gave	0.3924 $\text{Mg}_2\text{P}_2\text{O}_7$	= 100.25 per cent.
0.3176       "       "       "		0.388       "	= 99.76 per cent.
0.298       "       "       "	req.	48 C.c. standard	} = 99.88 per cent.
uranium acetate solution (1 C.c. = .005 $\text{P}_2\text{O}_5$ )			

This method having been proved accurate on pure material, it was consequently adopted.

The next experiments were made on a mixture of pure sodium hypophosphite with sodium phosphite.

This sodium phosphite on analysis was found to contain—

Sodium Phosphite.....	61.33 parts.
Sodium Phosphate .....	11.00 parts.
Sodium Carbonate.....	27.67 parts (by difference).

The mixtures thus made would approximate closely to the commercial article, and any other impurities present would either be removed by the lead acetate or would not interfere with the phosphate determination.

After many experiments the best way of carrying out the analysis was found to be as follows:—

About 0.3 gramme of the dried salt is dissolved in 10 C.c. of water, 3 C.c. of a 10 per cent. solution of lead acetate added, and the mixture allowed to stand twelve hours. It is then filtered, the precipitate thoroughly washed, and the washings added to the filtrate, which is acidified with hydrochloric acid, and then saturated with hydrogen sulphide, boiled, filtered, and the lead sulphide thoroughly washed.

The mixed washings and filtrate are then evaporated to a low bulk and 5 C.c. hydrochloric acid and 1 gramme potassium chlorate added and gently heated for half an hour, then concentrated to about 20 C.c., and the phosphate finally determined either gravimetrically or volumetrically by the usual method. The results were as follows:—

Composition of the Mixture.		Found.
Per cent. of $\text{NaPH}_2\text{O}_2$ present.....	{ 90.96	90.38
	{ 98.56	98.30

The method having been thus proved accurate within the usual

limits of experimental error, the method of qualitative examination was investigated.

The usual tests were made for metallic impurities, calcium, carbonate, sulphate, and phosphate. With regard to the latter, it must be remarked that the absence of a precipitate with magnesia mixture does not necessarily imply that no phosphate is present, as the test is not so delicate, but that it is certainly not present in more than traces. Attention is also directed to the test for chlorides. Contrary to general statements, it is not easy to completely oxidise this salt by means of nitric acid, and it is therefore necessary in carrying out this test to boil for at least five minutes with nitric acid, then add the silver nitrate and boil for another five minutes if any precipitate is formed. Phosphites and sulphites were tested for in the precipitate produced by lead acetate by the method described by Tyrer. Carbonate and moisture were estimated in the usual way. A series of parallel experiments were made on a sample of commercial sodium hypophosphite, using different methods of assay.

Method.	U.S.P.	Calomel.	Magnesia.	Uranium.
Pure Salt .....	101.1	101.3	99.76	99.68
Coml. Salt .....	92.85	92.69	91.40	91.65
				} per cent.

Whilst the results obtained by the uranium and magnesia methods agree, those obtained by the other methods show a higher percentage, due to errors of the method, and also to the presence of phosphite, which would give a high result.

**POTASSIUM HYPOPHOSPHITE.**—This salt is anhydrous and can be purified in a similar manner to the sodium salt, but this purification is a little more difficult, due to the limited solubility of the salt in alcohol. The quantitative and qualitative examination of this salt is carried out in a similar manner to the sodium salt, except that in the case of this hygroscopic salt the moisture is not determined.

The assay of a commercial sample by different methods gave a similar result to the sodium salt.

U.S.P. method.....	95.5 per cent.
Calomel „ .....	97.3 „
Magnesia „ .....	94.82 „
Uranium „ .....	94.42 „

**CALCIUM HYPOPHOSPHITE.**—This salt is not easily obtained pure,

and some commercial specimens do not form a clear solution with water. When the salt is crystallised from water by evaporation *in vacuo* at the ordinary temperature three separate fractions gave the reaction with lead acetate, consequently it is not possible to purify the salt by recrystallisation. It may, however, be prepared quite pure in the following manner:—To the aqueous solution is added lead acetate in slight excess, the mixture then filtered after standing twenty-four hours, and the filtrate saturated with hydrogen sulphide and filtered. The hydrogen sulphide is then removed by a current of air and the salt precipitated by the addition of alcohol to the aqueous solution. The pure salt crystallises in pearly flakes, which give no reaction with lead acetate.

Several contradictory statements have been made regarding the solubility of this salt in water. The U.S.P. gave 1 in 6·8, Tyrer 1 in 7·2, B.P. 1 in 8, and various text-books 1 in 6, but it is not clear whether these statements refer to the commercial article or the pure salt. Having in my possession a quantity of the pure salt, I determined its solubility and found it to be 1 in 6·43 parts of water at 20°. Of the commercial specimens examined, one only was soluble in 8 parts of water, and some did not form a clear solution even in 14 parts of water. Experiments of heating at 110° and boiling in pure water similar to those made with the sodium salt having shown that the calcium salt is quite stable under these conditions, the effect of evaporation of an aqueous solution of the pure salt under ordinary conditions was noted. A 10 per cent. solution of pure calcium hypophosphite was evaporated on a water bath to dryness, and the residue on analysis gave 97·73 per cent. of calcium hypophosphite. This may be a cause of the phosphite present in many commercial specimens. The specimen of the pure salt obtained commercially had an appearance which suggests precipitation from aqueous solution by alcohol. Another method of preventing this decomposition would be by evaporation *in vacuo*.

The method of analysis has to be slightly modified for the calcium salt on account of the insoluble calcium phosphate formed. If weighed as  $\text{Mg}_2\text{P}_2\text{O}_7$ , the best method is to proceed as with the sodium salt, then remove the lead and calcium as sulphate by precipitating with dilute sulphuric acid and adding alcohol. The further operations are the same as with the sodium



salt. A better method is to determine volumetrically by uranium acetate, following the usual precaution observed in the presence of calcium and carefully standardising the solution against pure calcium hypophosphite. Good results were obtained by both of these methods on the pure salt.

Found by $\text{Mg}_2\text{P}_2\text{O}_7$ method .....	100·35 per cent. }
Found by Uranium method .....	99·77 per cent. }
Found by U.S.P. ( $\text{KMnO}_4$ ) method ..	97·7 per cent.

With this salt the permanganate method gives results lower than the actual value.

#### COMMERCIAL CALCIUM HYPOPHOSPHITE—

Found by $\text{KMnO}_4$ , U.S.P. method .....	95·97 per cent.
Found by $\text{Mg}_2\text{P}_2\text{O}_7$ method .....	97·49 per cent.
Found by Uranium method .....	97·56 per cent.
Found by Calomel method .....	97·3 per cent.

**BARIUM HYPOPHOSPHITE.**—This salt can be assayed in the same way as the calcium salt, omitting the alcohol in the removal of the barium. The permanganate method here gives results higher than the actual value, as in the case of the sodium and potassium salts.

In a commercial specimen I found :—

By $\text{KMnO}_4$ method .....	98·6 per cent.
By $\text{Mg}_2\text{P}_2\text{O}_7$ method .....	97·25 per cent.
By Uranium method .....	97·29 per cent.

As the last two salts are used for the manufacture of hypophosphorous acid it follows that the acid will contain the same impurities as are present in them, such as phosphorous acid, etc. The acid can be determined by neutralising with sodium hydrate and proceeding as with sodium hypophosphite.

**MANGANESE HYPOPHOSPHITE,  $\text{Mn}(\text{PH}_2\text{O}_2)_2 \cdot \text{H}_2\text{O}$ .**—This salt is easily prepared by dissolving manganese carbonate in the equivalent quantity of hypophosphorous acid and crystallising from the hot aqueous solution. The purity of the salt will depend on the acid used. It crystallises with one molecule of water, and is somewhat difficult to determine. It cannot be done by the magnesia method, as the manganese cannot be completely removed, but good results were obtained with the uranium method by proceeding as with the calcium salt, but first removing the lead and most of the manganese by ammonium carbonate and ammonia.

In a sample prepared by myself from the commercial acid, I found 98·61 C.c. of manganese hypophosphite.

IRON HYPOPHOSPHITE.—This salt is official only in the U.S.P., and can be prepared by two distinct methods: (1) From ferrous sulphate and calcium hypophosphite by double decomposition, filtration, and evaporation of the filtrate, when a mixture of ferrous and ferric hypophosphites and phosphites with calcium sulphate is obtained; (2) from a soluble ferric salt and a hypophosphite by double decomposition, filtration, washing, and drying of the precipitate obtained. This product is chiefly ferric hypophosphite with a varying amount of impurity dependent on the purity of the materials used and the thoroughness of the washing. The qualitative and quantitative examination of these salts was carried out as follows:—The tests for calcium, sulphate, carbonate, and chloride, were made in the usual way, observing the precautions necessary, and detailed under sodium hypophosphite. Phosphite was detected by shaking up 0.5 gramme of salt with 10 C.c. of a 5 per cent. solution of sodium hydrate in the cold, filtering, acidifying the filtrate with acetic acid, and adding lead acetate. If much sulphate is present, it is necessary to further test the lead precipitate by reduction. Unfortunately I was unable to devise a method of determining the amount of hypophosphite present in this salt without introducing the error due to phosphite, but this can be partly remedied by noting the amount of lead precipitate in the test above detailed. The determination is then carried out on about 0.3 gramme of salt by first oxidising with potassium chlorate and hydrochloric acid in the usual way, then adding 0.5 gramme of sodium citrate and finally excess of pure sodium hydrate. The precipitate is washed thoroughly, the iron contained in it determined iodometrically, and the phosphate contained in the filtrate by the usual analytical methods. A blank experiment performed in this way on a mixture of pure ferrous sulphate and sodium hypophosphite gave—

	Calculated.	Found.
Iron .....	20.14 per cent.	20.35 per cent.
Ferric Hypophosphite ..	100.00 per cent.	99.92 per cent.

These results prove the accuracy of the method, and it may be noted that the presence of phosphite would affect both the iron and phosphate determinations.

Being thus in the possession of a reliable method of assay, I made some specimens of ferrous and ferric hypophosphites by different methods and examined the resulting product.

I first prepared a salt by mixing solutions of equivalent proportions of ferrous sulphate and calcium hypophosphite, filtering and then evaporating to dryness on a water bath. In this way a greenish-grey powder was obtained which contained ferrous and ferric hypophosphite with some phosphite and calcium sulphate.

On analysis the salt gave :—

Ferric Hypophosphite .....	71.02 per cent.
By U.S.P. . . . .	74.95 per cent.
Iron . . . . .	22.06 per cent.
Calcium Sulphate .....	13.8 per cent.

This was obviously a very unsatisfactory product, so the calcium hypophosphite was replaced by the barium salt, and a reddish powder was obtained which on analysis gave :—

Ferric Hypophosphite .....	91.52 per cent.
By U.S.P. . . . .	89.5     "
Iron . . . . .	28.88     "
Barium or Sulphate .....	nil.

If these results are calculated as ferrous hypophosphite the amount present is 102.26 per cent., so that the product consists of ferrous with a little ferric hypophosphite, and some phosphite. This preparation would appear to be satisfactory but for its indefinite composition; recourse was had, therefore, to the ferric salt. This salt was prepared by double decomposition of ferric sulphate (iron alum) or ferric chloride and sodium hypophosphite. The precipitate was washed, but it is very difficult to wash thoroughly without a very serious loss of the hypophosphite, and the salt therefore generally contains a certain amount of this impurity dependent on the salts used. If calcium chloride is present, the salt will be deliquescent, as stated by Tyrer, but some prepared by myself from iron alum was quite stable in the air. The results of the examination of several commercial specimens showed that both the sulphate and chloride are used in the manufacture of this salt.

A sample prepared from ferric sulphate gave on analysis :—

Ferric Hypophosphite . . . . .	94.25 per cent.
U.S.P. method . . . . .	88.25     "
Iron . . . . .	22.27     "
Sodium Sulphate .....	4.17     "

This sample contained no ferrous iron, and was a white amorphous powder. The above experiments show that the permanganate method of the U.S.P. does not give accurate results, whilst its use is inadmissible with the ferrous salt. It is clear from these experi-



ments that the best salt is the ferrie hypophosphite, which should be used, and not the mixture prepared from a ferrous salt.

EXAMINATION OF COMMERCIAL SPECIMENS.—Having worked out a satisfactory and accurate method of assay for these salts, specimens of the sodium, potassium, calcium, and iron salts were obtained from two leading English manufacturers and also from three leading American houses, and examined according to the method previously detailed.

The English manufactured products are designated B1, B2, and those of American manufacture A1, A2, A3. Of these A1 was sold as purified, the others had the name of the salt only on the label.

#### SODIUM HYPOPHOSPHITE.

Sample.	$\text{Na}_2\text{CO}_3$ .	Moisture	$\text{NaPH}_2\text{O}_2$ percent. of dried salt.	Impurities.
B1 .....	0.16	3.19	91.52	Phosphite, traces $\text{Ca}, \text{'SO}_4, \text{'Cl}, \text{'CO}_3$ . Phosphite, traces $\text{Ca}, \text{'SO}_3, \text{'SO}_4, \text{'Cl}, \text{'CO}_3$ . Traces phosphite, $\text{'CO}_3, \text{'Cl}, \text{'SO}_4$ Phosphite, traces, $\text{Ca}, \text{'SO}_4, \text{'Cl}, \text{'CO}_3$ ditto
B2 .....	0.08	9.92	96.97	
A1 .....	0.09	14.41	99.78	
A2 .....	0.79	1.32	96.53	
A3 .....	0.36	4.09	98.26	

Of these specimens A1 is pure and represents the hydrated salt, the others contain varying amounts of moisture and impurities, the chief being sodium phosphite. The traces of calcium, sulphate, chloride and carbonate present are no doubt derived from the sodium carbonate and calcium salt used in the manufacture.

#### POTASSIUM HYPOPHOSPHITE.

Sample.	$\text{K}_2\text{CO}_3$ .	$\text{KPH}_2\text{O}_2$ . Per cent. of dried salt.	Impurities.
B1 .....	2.8	94.62	Phosphite, traces $\text{Ca}, \text{'SO}_4, \text{'Cl}$
B2 .....	0.4	98.06	Phosphite, traces $\text{Ca}, \text{'Cl}, \text{'SO}_4, \text{'SO}_3$
A1 .....		98.11	Phosphite, traces $\text{'SO}_4, \text{'Cl}$
A2 .....	3.72	92.52	Phosphite, traces $\text{'SO}_4$
A3 .....	0.68	98.51	Phosphite, traces $\text{Ca}, \text{'Cl}'$

Here the impurities present are similar to those found in the sodium salt, but there is an excessive amount of  $\text{K}_2\text{CO}_3$  in two samples. No sample is as pure as the A1 sodium salt, which must be due to the mode of manufacture. I have before noted that this salt is not so easily purified as the sodium salt. Sulphites, about

which some contradictory statements have been made, were present in one sample only, viz., B2.

#### CALCIUM HYPOPHOSPHITE.

Sample.	Per cent. of $\text{Ca}(\text{PH}_2\text{O}_2)_2$ .	Impurities.
B1 .....	97.50	Phosphite and sulphate.
B2 .....	98.18	Traces iron, phosphite, and sulphate.
A1 .....	99.37	Traces phosphite.
A2 .....	97.64	Phosphite and sulphate.
A3 .....	99.61	Nil.

Of these A3 was perfectly pure and readily soluble in 8 parts of water; the others were not soluble in this amount, and B1 and A2 did not give a clear solution even with 20 parts of water. B2 contained an appreciable trace of iron, the only metallic impurity met with in the whole series.

#### IRON HYPOPHOSPHITE.

Sample.	Iron. per cent.	Ferric Hypophosp. per cent.	Impurities.
B1 .....	22.34	84.12 (Ferrous)	12 p.c. $\text{CaSO}_4$ , phosphite and $\text{Cl}'$
B2 .....	21.96	89.84	Phosphite, traces Ca, $\text{Cl}'$
A1 .....	22.54	98.84	Phosphite, traces Ca and $\text{SO}_4''$
A2 .....	23.00	95.02	Phosphite, traces Ca and $\text{SO}_4''$
A3 .....	20.20	87.58	9 p.c. $\text{Na}_2\text{SO}_4$ , phosphite and $\text{Cl}'$

B1 was chiefly ferrous hypophosphite, and had evidently been prepared from ferrous sulphate and calcium hypophosphite, and agreed closely with that prepared by myself. The others were true ferric hypophosphite, B2 apparently prepared from ferric chloride, and the others from a ferric sulphate. A3 was very insufficiently washed, and compared very unfavourably with the other salts of this make.

As a result of this work, I would suggest as worthy of the consideration of various Pharmacopœia Revision Committees the necessity of a thorough revision of the tests for these salts and the need of fixing some standard which might be as follows:—For the calcium and barium salts, 98 per cent.; for the sodium and potassium salts, 96 per cent.; for ferric salt, 95 per cent. As a suggestion for the tests, I give below those for sodium hypophosphite based, it will be seen, on the system of the U.S.P., which I consider preferable, on the whole, to that of the present B.P.

SODIUM HYPOPHOSPHITE,  $\text{NaPH}_2\text{O}_2$ .—5 C.c. of a 5 per cent. solution (to be used of this strength in the following tests) should

yield, with 1 drop AmHS, no colour or turbidity (absence of metallie impurities).

5 C.e. with 1 C.c.  $\text{Am}_2\text{C}_2\text{O}_4$  test solution, and 1 C.e. acetic acid, should yield not more than a slight opalescence (limit of calcium).

5 C.e. with 1 C.e.  $\text{BaCl}_2$  test solution, and 1 C.c. HCl, and boiled for two minutes, should yield no preeipitate (limit of sulphate).

5 C.e., boiled for five minutes with 5 C.c.  $\text{HNO}_3$ , and then 1 C.e.  $\text{AgNO}_3$  test solution added, and again boiled for five minutes, should yield no turbidity (absence of chloride).

5 C.e., with 5 C.c. magnesia mixture, and well shaken, should yield no precipitate (limit of phosphate).

1 gramme of the dried salt, dissolved in water, to which is added 0.5 C.c. of N/10  $\text{H}_2\text{SO}_4$ , with 1 drop of phenol-phthalein solution, should remain colourless (limit of carbonate = 0.2 per cent.)

When analysed as before described, should yield 96 per cent. of sodium hypophosphite.

A simple test which could be used would be the following :—To 1 gramme of the dried salt, dissolved in 10 C.e. of water, add 9 C.c. of a 1 per cent. solution of lead acetate, allow the mixture to stand for half an hour, and filter. On adding lead acetate to the filtrate the liquid should remain quite clear. This corresponds to about 96 per cent. of pure sodium hypophosphite.

In conclusion, I have added a list of the factors necessary in making analyses by these methods and the corresponding logarithms, these being based on the atomic weights of Meyer and Seubert, in the hope that they may be useful to any who may use these methods of analysis.

TABLE OF FACTORS FOR USE IN ANALYSIS.

Salt.	M. Wt.	$\text{Mg}_2\text{P}_2\text{O}_7$ .		1 C.c. Uran. Sol. = 0.005 $\text{P}_2\text{O}_5$ .	
		Factor.	L. Factor.	= grammes.	L. grammes.
Sodium hypophosphite ..	87.88	0.79085	$\overline{1}$ .89810	0.0062	$\overline{3}$ .79246
Potass. „ ..	103.91	0.9351	$\overline{1}$ .97087	0.0073	$\overline{3}$ .86523
Calcium „ ..	169.67	0.76346	$\overline{1}$ .88279	0.006	$\overline{3}$ .77714
Barium „ ..	266.66	1.11999	0.07914	0.0094	$\overline{3}$ .97350
Manganese „ (hydrated) ..	202.52	0.9113	$\overline{1}$ .95965	0.0071	$\overline{3}$ .85401
Ferrie „ ..	501.04	0.7515	$\overline{1}$ .87593	0.0077	$\overline{3}$ .77029
Ferrous „ ..	185.64	0.8353	$\overline{1}$ .92185	0.0065	$\overline{3}$ .81621
Hypophosphorous acid .	65.88	0.5929	$\overline{1}$ .77297	0.0046	$\overline{3}$ .66732
Anhyd. Mn. $(\text{PH}_2\text{O}_2)_2$ . . . .	184.56	0.83045	$\overline{1}$ .91932	0.0065	$\overline{3}$ .81368

The above experiments were carried out in the Wellcome Research Laboratory, London, E.C.



# NOTE ON THE MYDRIATIC ALKALOIDS.\*

BY

H. A. D. JOWETT, D.Sc.

That some confusion should have arisen in the past regarding this group of alkaloids is not altogether surprising, considering that there was on the market a variety of products designated daturine, duboisine, heavy and light atropine, etc., and that the literature of the subject was in a most unsatisfactory condition. The work of Schmidt and others has, however, removed these discrepancies, and it is now possible to obtain in commerce products of definite chemical composition of a high degree of purity. A paper read by Dr. G. Sharpe at last year's Conference (*P. J.*, 1897, p. 160) contained several statements and conclusions which are not in accord with our present knowledge of this subject, and in the 1898 B.P. the description and tests of the official members of this group are generally unsatisfactory, and in some cases misleading and inaccurate. I therefore thought that it would not be without interest to the members to contribute a short note on the subject.

As Dr. Sharpe says, the several names which have been used for a mixture of these alkaloids, as daturine, duboisine, light atropine, etc., should be once and for all abandoned, as they only represent a variable product obtained from a particular plant, the composition of the product depending on the process of manufacture, but consisting chiefly of atropine or hyoscyamine. The only alkaloids belonging to this group which can at present be definitely considered as chemical entities are atropine, hyoscyamine, and scopolamine. These are bodies of definite composition, whose chemical and physical properties have been carefully studied. In addition to these bases pseudo-hyoscyamine, from *Duboisia myoporoides*, isomeric with atropine and hyoscyamine, has been

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\* Read at the British Pharmaceutical Conference, 1898, and reprinted from the PHARMACEUTICAL JOURNAL, August 13, 1898.

described by Merck, but its relation to its isomers has not yet been worked out.

ATROPINE.—Atropine can be prepared either synthetically from tropine and tropic acid by the elimination of water, or by isomeric change from hyoscyamine. The alkaloid contained in belladonna root and other solanaceous plants is primarily hyoscyamine, which, during the processes of extraction, precipitation, etc., becomes converted into atropine by the action of the heat and alkali used. Atropine itself is present in only a very small amount, if at all, in these plants. Dr. Sharpe states that "the relationship of these two bases can hardly be said to be understood," but this statement requires a little modification. Though the nature of the isomerism of these two bases is not at present known, their properties are such as to differentiate them sharply from each other, and it is certainly within the ability of the chemist to detect these differences.

The best and simplest test for determining the freedom of atropine from hyoscyamine or scopolamine is its optical inactivity, both the other bases and their salts being optically active. The presence of a small amount of these likely impurities would thus be at once detected. The new B.P., in the tests for atropine and the sulphate, makes no mention of this fact, but it is stated amongst the characters and tests of aconitine that it is dextro-rotatory, which is perfectly true, but the object of this statement is not apparent, as this property is no test of either its identity or purity. Beyond the melting points the B.P. gives no test for the presence of organic impurities in atropine or its sulphate. That of the base ( $115.5^{\circ}$ ) is correct for a pure product, but that given for the sulphate ( $183^{\circ}$ ) is open to criticism. Will (*Ber.*, 21, p. 1724) gives it as  $196^{\circ}$ , the U.S.P.  $187^{\circ}$ , Hesse (*A.*, 271, p. 102),  $180^{\circ}$ - $181^{\circ}$ , Merck  $189^{\circ}$ - $191^{\circ}$ , whilst a salt, proved to be optically inactive, prepared by myself from pure atropine melted at  $190^{\circ}$ . A good commercial specimen melted at  $190^{\circ}$ , so that there is no doubt but that the B.P. melting point is too low.

The sulphate can always be obtained quite white, but has generally an amorphous appearance though really crystalline, and here again the pharmacopœial description requires modification. The melting points of the aurichlorides of this group form a very easy way of identifying the alkaloid and also afford some criteria as to its purity. The B.P. recognises these salts and gives the

melting point for scopolamine aurichloride, but by a strange inconsistency not those of atropine and hyoscyamine, where it relies on the appearance of the salt, of which again a misleading account is given. They are best prepared by dissolving the base in excess of hydrochloric acid, then adding auric chloride and crystallising from the hot solution. The B.P. gives an impracticable method of preparing it from an aqueous solution of atropine. The appearance of the two salts is very characteristic; the atropine aurichloride separates first as an oily clot, which solidifies to a crystalline mass, the hyoscyamine salt comes down in brilliant golden-yellow crystals. The melting points are very sharp and separated by  $23^{\circ}$ . Atropine aurichloride melts at  $137^{\circ}$ , and hyoscyamine aurichloride at  $160^{\circ}$ . The B.P., therefore, requires in this respect amendment and addition. The insertion of the colour test with fuming nitric acid and potash is quite unnecessary, and as tests for identity and purity of the base and salts I would suggest—

1. Melting point.
2. Formation and melting point of the aurichloride.
3. Optical inactivity.
4. Freedom from ash on ignition.

These tests would ensure a pure product, and one which can reasonably be expected from the manufacturer.

**HYOSCYAMINE.**—This base is actually found in many solanaceous plants, including belladonna, scopolia, etc., and not “possibly” as the B.P. states. It is optically active, and can be converted quantitatively by heat or by treatment with alkali into atropine. It is not, however, only an optical isomer of atropine, as lævo-atropine has been prepared synthetically and is not identical with hyoscyamine. It is distinguished from atropine by its optical activity and by the melting point of its aurichloride ( $160^{\circ}$ ). The melting point of the sulphate as it occurs in commerce is about  $200^{\circ}$ , whilst I have found the pure salt to melt at  $204^{\circ}$  and not, as stated in the B.P., at  $206^{\circ}$ . I would suggest a melting point of *not lower than*  $200^{\circ}$ .

**SCOPOLAMINE (HYOSCINE).**—This base is found accompanying hyoscyamine in very small quantity (0.03 per cent.) in many solanaceous plants, its chief source being *Scopola atropoides*. It is distinguished from both atropine and hyoscyamine by several well-marked characteristics, the most important of which are its per-



centage composition, its products of hydrolysis, and the melting points of its salts, particularly the aurichloride. Lately Schmidt has shown that it exists in stereo-isomeric forms, differing in optical activity and slightly in melting points, but not in their physiological action.

It is identical with the base called hyoscine, prepared from hyoscyamus seed, but this is not the source of the commercial article, which is preferably called scopolamine. This question has, however, been very recently discussed by Schmidt, Hesse, and Merck, and may be considered satisfactorily settled. The characters and tests given for the hydrobromide in the B.P. are very unsatisfactory.

The solubility in water (1 in 1) is incorrect. The U.S.P. gave 1 in 1.9, and Hesse gives 1 in 4, which is more correct. The hydrated salt, when heated (in a capillary tube) to  $100^{\circ}$ , forms a clear liquid, and no alteration can be observed on further heating to  $181^{\circ}$  (the melting point of the dehydrated salt). The statement in the B.P., therefore, is somewhat misleading.

The melting point of the dehydrated salt as there given ( $193^{\circ}$ - $194^{\circ}$ ) requires modification. According to Schmidt (*Arch. Ph.*, 236, pp. 47, *et seq.*) the scopolamine hydrobromide of commerce consists of a varying mixture of lævo (or normal) and inactive scopolamine in proportions dependent on the source of the alkaloid and the mode of manufacture. The commercial salt has a specific rotatory power of about  $-13^{\circ}$ , and melts at  $181^{\circ}$ . The purified lævo salt melts at  $193^{\circ}$ , and the inactive modification at  $180^{\circ}$ , but it has been shown that there is no difference in the physiological action of these salts. The tests and characters of the official salt should therefore be given for the pure product as it appears in commerce, which is a mixture of the stereo-isomers, melting at  $181^{\circ}$ . This is the melting point given by Hesse and confirmed by my own experiments. It would be interesting to know if the compilers of these tests have met with a salt in commerce of the melting point given ( $193^{\circ}$ - $194^{\circ}$ ).

With auric chloride the salt is stated to give a crystalline salt melting at  $198^{\circ}$ , which is not correct. As I have previously shown (*J. C. S.*, 1897, p. 679), an additive compound is formed under these conditions of the formula  $B \cdot HBr \cdot AuCl_3$ , which melts at  $215^{\circ}$ . The aurichloride, when prepared in the usual manner, melts sharply at  $198^{\circ}$ , thus differentiating it from atropine and hyoscyamine. There does not seem to be any reason why the salt

should not be neutral to litmus, as a properly prepared salt will conform to this condition. The statements of Dr. Sharpe regarding hyoscine and scopolamine show that he has confused these bases, but if the investigations made in recent years be considered, it will be found that our knowledge of this group of alkaloids is quite definite and satisfactory.







